

①②

EUROPEAN PATENT APPLICATION

②① Application number: 87106496.0

⑤① Int. Cl. 4: B01J 39/04 , A61K 9/18

②② Date of filing: 05.05.87

Claims for the following Contracting States: AT
+ GR + ES.

③② Priority: 30.07.86 US 892168

④③ Date of publication of application:
03.02.88 Bulletin 88/05

⑥④ Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

⑦① Applicant: PENNWALT CORPORATION
Pennwalt Building Three Parkway
Philadelphia Pennsylvania 19102(US)

⑦② Inventor: Chow, San-Laung
4 Shagbark Way
Fairport New York 14450(US)
Inventor: Raghunathan, Yegnaswami
6 Dunham Circle
Fairport New York 14450(US)

⑦④ Representative: Kraus, Walter, Dr. et al
Patentanwälte Kraus, Weisert & Partner
Thomas-Wimmer-Ring 15
D-8000 München 22(DE)

⑤④ Polymer-treated ion exchange resins.

⑤⑦ Sulfonic acid cationic exchange resin particles which have been treated to improve their coatability with minor amounts of high molecular weight polymers selected from carboxypolymethylene, xanthan gum, and propylene glycol alginate.

EP 0 254 822 A2

POLYMER-TREATED ION EXCHANGE RESINS (IR 2819)

The present invention relates to sulfonic acid cationic exchange resin particles which have been treated with a minor amount of a high molecular weight polymer to improve the particles coatability, and to selective, prolonged continuous release pharmaceutical preparations made therefrom. As described in U.S. Patent No. 4,221,778, the contents of which are incorporated herein by reference, such preparations contain ion exchange resin particles having a pharmacologically active drug adsorbed thereon to form drug-resin complex particles, at least a portion of which particles are treated with an impregnating agent and provided with a diffusion barrier coating.

10 BACKGROUND

U.S. Patent No. 4,221,778 discloses that controlled (i.e., selective, prolonged) continuous release of pharmacologically active drugs, under conditions such as those encountered in the gastrointestinal tract, can be achieved by the application of diffusion barrier coatings to ion exchange resin drug complex particles which have been treated, prior to coating, with an impregnating agent selected from polyethylene glycol, propylene glycol, mannitol, lactose, and methylcellulose.

BRIEF SUMMARY OF THE INVENTION

20 The present invention is concerned (a) with sulfonic acid cationic exchange resin particles which have been treated to improve their coatability with up to about 1.1 percent by weight (based on the combined weight of the particles and the polymeric treating agent) of an effective amount of a high molecular weight polymer selected from carboxypolymethylene, xanthan gum, and propylene glycol alginate, (b) with such resin particles which have a basic drug adsorbed thereon to form drug-resin complex particles, (c) with such drug-resin complex particles which have been coated, subsequent to treatment with the polymer, with a water-permeable diffusion barrier, and (d) with pharmaceutical preparations comprised of such coated drug-resin complex particles. Prolonged continuous release of the drug is obtainable from such preparations under conditions encountered in the gastrointestinal tract.

30 By varying the amount of coating, and/or by blending coated drug-resin complex particles with uncoated drug-resin complex particles, it is possible to selectively modify the preparation's drug dissolution profile as desired.

The ion exchange resins, drugs, and coatings, and methods for preparing drug-resin complexes, for coating of the complexes, and for selectively modifying the preparation's dissolution profile through blending and/or degree of coating, are disclosed and exemplified in U.S. Patent No. 4,221,778, said disclosure and examples being herein incorporated by reference.

DETAILED DESCRIPTION

40 While U.S. Patent 4,221,778 disclosed that about 10 to 25% by weight of a treating agent was normally needed to improve the resin's coatability, it has now been found that the aforementioned polymeric treating agents of this invention need only be used in amounts of up to about 1.1 percent by weight, based on the weight of the resin and the polymer (equivalent to about 0.8 percent by weight based on the weight of the drug-resin complex and the polymer). The carboxypolymethylene (such as Carbopol® 934P, described by the manufacturer as a high purity grade acrylic acid polymer having a molecular weight of approximately 3,000,000) is normally used at a level of from about 0.1 to about 1.1% by weight (preferably 0.4 to 0.8%); the xanthan gum is normally used at a level of from about 0.04 to about 0.20% by weight (preferably 0.07 to 0.16%); and the propylene glycol alginate is normally used at a level of from about 0.3 to about 0.9% by weight (preferably 0.5 to 0.7%); all such percentages being based on the combined weight of the resin and the polymer. As shown in Table I hereinafter, treatment of the resin with the polymers of this invention (Examples 1 to 3), in comparison to untreated resin (Comparative Example), enhanced the resin's coatability as evidenced by the significantly greater retardation in the drug release rate in the coated drug-resin complexes made from the treated resin.

In general, all pharmacologically active basic drugs, especially those having short biological half-lives in the order of up to about eight hours, are potential candidates for inclusion in the subject preparations. Examples include, but are not limited to, phenylpropanolamine (PPA), dextromethorphan, codeine, hydrocodone, hydralazine, propranolol, doxepin, metaproterenol, morphine, ephedrine, pseudophedrine, and verapamil. PPA, a sympathomimetic amine drug with a biological half life of 3.9 hours in man and a pK_a of 9.4, was chosen as a model drug for use in the illustrative examples. The loading of the drug on the resin particles can be from about 1 to about 90 percent by weight, although 15 to 50 percent is the normal practical range.

The resin is a sulfonic acid cationic exchange resin, normally in particle sizes ranging from about 25 to about 1000 μm . The illustrative examples employ Amberlite® IRP-70 resin, a cationic exchange resin which is 100-200 mesh (75-150 μm) fractured resin particles of Amberlite IR-120. The parent resin of Amberlite IR-120 and Amberlite IRP-70 is described by the manufacturer as a gel-type divinylbenzene sulfonic acid cationic exchange resin which swells in water with a pH range of 0-14. The resin should not have inherent pharmacological or toxic properties.

Adsorption of the drug onto the ion exchange resin particles to form the drug resin complex is a well known technique as shown in U.S. Patent Nos. 2,990,332 and 4,221,778. In general the drug is mixed with an aqueous suspension of the resin, and the complex is then washed and dried. Adsorption of drug onto the resin may be detected by a change in the pH of the reaction medium.

The water-permeable, diffusion barrier coating material can in general be any of the conventional synthetic or natural film-forming materials with diffusion barrier properties and with no inherent pharmacological or toxic properties. Ethylcellulose, a water insoluble film-forming agent was used as the model diffusion barrier membrane material in the illustrative examples. A plasticizer, Durkex® 500 vegetable oil, was used to improve the film-forming characteristics of ethylcellulose. The amount of coating used depends on the degree of drug release prolongation desired.

Conventional coating solvents (such as ethanol, or a methylene chloride/acetone mixture, or coating emulsions) and coating procedures (such as fluid bed coating) can be employed to coat the particles. Techniques of fluid bed coating are taught, for example, in U.S. Patent Nos. 3,089,824; 3,117,027; and 3,253,944. The coating is normally applied to the drug resin complex, but alternatively can be applied to the resin before complexing with the drug.

In the examples to follow the drug-resin complex particles are coated at a level of 16 percent by weight (as dry weight of the non-volatile solids of the coating, complex, and treating agent, if any) with a coating solution containing about 5% by weight ethylcellulose (50cps), about 2% by weight Durkex 500 refined vegetable oil, about 10% by weight acetone, and the balance methylene chloride. The coating solution is prepared by dissolving the Durkex and ethylcellulose in the acetone and methylene chloride. The coating of the complex particles is carried out in a fluid bed coating apparatus at a rate of 16-17 ml of coating solution per minute. The inlet air temperature is about 33°C and the outlet air temperature is about 22-25°C.

As shown in the control test below (Control), an untreated and uncoated resin-drug complex rapidly releases its drug (86.5% in 30 minutes) in a simulated gastric fluid (0.1 normal hydrochloric acid). Coated, but untreated, complex particles (Comparative Example) partially retard this release rate (30.9% release of drug in 30 minutes), but the release rate is further retarded (16.1-21.0% release in 30 minutes) when the complex particles are treated with polymeric agents prior to coating (Examples 1-3). While the polymer is normally applied to the complex, it may be applied to the resin particles prior to complexing, as in the case where the resin particles are coated prior to complexing with the drug. In the following examples the polymeric agent, dissolved in sufficient deionized water, is added to the PPA-resin complex and mixed (in a suitable planetary mixer) for about 10 minutes, then fluid bed dried to a moisture of less than 5%.

Variation in the amount of coating and/or the use of coated/uncoated complex mixtures can be employed to selectively modify the dissolution profile as desired. In addition to oral administration, the preparations of the subject invention are also suitable for topical, rectal or vaginal administration in dosages varying over a wide range, for example, from about 0.1 to about 1000 mg, depending on the nature of the drug and its intended usage. The compositions can take the form of tablets, powders, capsules, liquid suspensions or other conventional dosage forms.

The following dissolution test apparatus and procedures are used in the examples to simulate conditions encountered in the gastrointestinal tract: Five hundred ml of the dissolution medium (0.1N HCl) is placed in a round bottom flask immersed in a suitable water bath and the temperature allowed to rise to 37±0.5°C. The flask is equipped with a paddle which is agitated at 100 rpm. The dissolution medium is pumped from the vessel through a cotton filter. Polyethylene tubing carries the filtered media via a peristaltic pump through a 1 cm flow cell of a Beckman model 35 recording spectrophotometer (equipped with a cell changer) and returns it to the vessel. The flow rate is adjusted to 16 ml/minute. In this way, each

of the six vessels and a standard can be monitored at 15 minutes or other suitable intervals. The spectrophotometer is operated at 257 nm in a single beam mode to monitor six resin complex samples and one PPA hydrochloride standard. Each dissolution vessel contains resin complex sample equivalent to 90.6 mg of PPA base. The standard PPA solution contains 90.6 mg of PPA based in 500 ml of 0.1 N HCl. The drug released is then expressed as a percentage of the total drug present in the complex particles.

ILLUSTRATIVE EXAMPLES

10 Control - Uncoated, Untreated Complex:

PPA hydrochloride (96.84 kg) was dissolved in 850 liters of deionized water in a glass-lined mixing kettle. Amberlite IRP-70 resin (243.77 kg), washed hydrogen cycle, was then added to the stirring PPA hydrochloride solution. The mixing was continued for 2 hours. The PPA-resin slurry was then transferred to the holding tank and then to the centrifuge. The resin core was washed with deionized water for at least 10 minutes until free of chloride ions. The resin core was then dried to a moisture of less than 5% in a fluid bed dryer having a 70°C inlet air temperature. The dried resin complex was found to contain 23.8% of phenylpropanolamine. Dissolution results are shown in Table I.

20

Comparative Example - Coated, Untreated, Complex:

Dissolution results on the PPA-resin complex particles, coated as described hereinabove, are shown in Table I.

25

Examples 1 to 3 - Pretreated, Coated Complex:

Three batches of coated PPA-resin complex particles were prepared, one of which was pretreated with about 0.8% Carbopol 934P (Example 1), one with about 0.07% xanthan gum (Example 2), and one with about 0.7% propylene glycol alginate (Example 3), all percents being by weight based on the weight of the resin and the polymer. The dissolution results are shown in Table I.

Table I

	% PPA Released At:			
	<u>0.25 hr.</u>	<u>0.5 hr</u>	<u>1.0 hr.</u>	<u>3.0 hr.</u>
Control	86.4	86.5	86.4	93.0
Comparative Example	21.0	30.9	41.7	58.1
Example 1	15.9	21.0	29.4	41.2
Example 2	14.2	20.9	25.3	43.7
Example 3	11.4	16.1	20.9	37.7

Applying the foregoing discovery, controlled release dosage forms can be formulated for human or veterinary use to contain suitable mixtures of coated and uncoated complex particles such that a desired controlled release profile of the drug is obtained. The dosage forms can be solid (such as powders, capsules and tablets) or liquid (such as a suspension of complex particles in a palatable vehicle).

55

Claims

1. Sulfonic acid cationic exchange resin particles which have been treated to improve their coatability with up to about 1.1 percent by weight of a high molecular polymer, based on the combined weight of the polymer and the particles, said polymer being selected from the group consisting of carboxypolymethylene, xanthan gum, and propylene glycol alginate.
2. Resin particles as in Claim 1 which have a basic drug adsorbed thereon to form drug-resin complex particles.
3. Drug-resin complex particles as in Claim 2 which have been coated, subsequent to treatment with the polymer, with a water-permeable diffusion barrier.
4. Pharmaceutical preparations comprised of the coated drug-resin complex particles of Claim 3.
5. The preparation of Claim 4 wherein the polymer is carboxypolymethylene.
6. The preparation of Claim 4 wherein the polymer is xanthan gum.
7. The preparation of Claim 4 wherein the polymer is propylene glycol alginate.

CLAIMS for the following Contracting States AT, GR and ES:

1. Sulfonic acid cationic exchange resin particles which have been treated to improve their coatability with up to about 1.1 percent by weight of a high molecular polymer, based on the combined weight of the polymer and the particles, said polymer being selected from the group consisting of carboxypolymethylene, xanthan gum, and propylene glycol alginate.
2. A process for the production of drug-resin complex particles comprising adsorbing a basic drug on the resin particles of Claim 1.
3. The process of Claim 2, characterized in that the drug-resin complex particles have been coated with a water-permeable diffusion barrier subsequent to treatment with the polymer.
4. The process of Claims 2 and 3, wherein the polymer is carboxypolymethylene.
5. The process of Claims 2 and 3, wherein the polymer is xanthan gum.
6. The process of Claims 2 and 3, wherein the polymer is propylene glycol alginate.

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets

(11) Publication number:

**0 254 822
A3**

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 87106496.0

(51) Int. Cl.4: **B01J 39/04 , A61K 9/18**

(22) Date of filing: 05.05.87

(30) Priority: 30.07.86 US 892168

(43) Date of publication of application:
03.02.88 Bulletin 88/05

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(88) Date of deferred publication of the search report:
05.04.89 Bulletin 89/14

(71) Applicant: **PENNWALT CORPORATION**
Pennwalt Building Three Parkway
Philadelphia Pennsylvania 19102(US)

(72) Inventor: **Chow, San-Laung**
4 Shagbark Way
Fairport New York 14450(US)
Inventor: **Raghunathan, Yegnaswami**
6 Dunham Circle
Fairport New York 14450(US)

(74) Representative: **Kraus, Walter, Dr. et al**
Patentanwälte Kraus, Weisert & Partner
Thomas-Wimmer-Ring 15
D-8000 München 22(DE)

(54) **Polymer-treated ion exchange resins.**

(57) Sulfonic acid cationic exchange resin particles which have been treated to improve their coatability with minor amounts of high molecular weight polymers selected from carboxypolymethylene, xanthan gum, and propylene glycol alginate.

EP 0 254 822 A3



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 87 10 6496

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
D, Y	US-A-4 221 778 (Y. RAGHANATHAN) * Column 2, line 41 - column 3, line 6; claims 1-3 *	1-7	B 01 J 39/04 A 61 K 9/18
Y	EP-A-0 171 528 (PENNWALT CORP.) * Page 3, line 10 - page 4, line 6; claims 1-4 *	1-7	
Y	US-A-3 594 470 (S. BORODKIN et al.) * Column 2, lines 50-72; column 3, lines 42-58 *	1-7	
A	GB-A- 982 150 (GLAXO GROUP LTD) * Page 2, lines 8-70 *		
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			A 61 K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 25-01-1989	Examiner TZSCHOPPE, D.A.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			